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| EXAMINER | |
|---|---|
| DUNSTON, JENNIFER ANN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1636 | |

DATE MAILED: 06/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/705,757 | WEIHE ET AL. | |
| | Examiner | Art Unit | |
| | Jennifer Dunston | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-16,19-21,26-28,32-36,40,43,46,47,53,57 and 64* is/are pending in the application.

4a) Of the above claim(s) *16,19-21,26-28,35,36,40,43,46,53,57 and 64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,32-34 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Appendix I*.

## DETAILED ACTION

This action is in response to the amendment, filed 3/29/2006, in which claims 17-18, 22-25, 29-31, 37-39, 41-42, 44-45, 48-52, 54-56, 58-63 and 65-82 were canceled, and claims 32-34 were amended. Currently, claims 1-16, 19-21, 26-28, 32-36, 40, 43, 46-47, 53, 57 and 64 are pending. Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

### *Election/Restrictions*

Applicant elected Group I, the sequences of PIM-1 kinase (SEQ ID NOS: 1-6), and the polynucleotides and cells of claim 36[a-c, f(a-d)] in the reply filed on 8/18/2005, with traverse.

Claims 16, 19-21, 26-28, 35-36, 40, 43, 46, 53, 57 and 64 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/18/2005. An examination of claims 1-15, 32-34 and 47 as they read on the elected invention follows.

This application contains claims 16, 19-21, 26-28, 35-36, 40, 43, 46, 53, 57 and 64 drawn to an invention nonelected with traverse in the reply filed 8/18/2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

### *Claim Objections*

Claims 1-12, 32-34 and 47 are objected to because of the following informalities: the claims read on non-elected inventions.

### *Response to Arguments*

Applicant's arguments, see page 17, filed 3/29/2006, with respect to the objection of claim 32 have been fully considered and are persuasive. The previous objection of claim 32 has been withdrawn.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 and 32-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection was made in the Office action, mailed 11/1/2005, and is reiterated below.

Claim 1 is vague and indefinite in that the metes and bounds of the claimed method are unclear. The preamble recites "a method for detecting a pain-regulating substance." However, it is not clear that measuring the binding of the test substance to a protein or part protein synthesized by the cell or measuring at least one functional parameter modified by the binding of the test substance to the protein or part protein will *necessarily* result in the identification of pain-regulating substances. The method steps encompass the testing of proteins defined by

percent identity, hybridization and fragments of the elected PIM-1 kinase, yet the claims do not require that the proteins or part proteins encompassed by the claimed method have any particular functional activity. Further, any functional parameter may be modified, and it is not clear that any parameter will necessarily relate to the identification of pain-regulating substances. Therefore, it is unclear if one necessarily accomplishes what is intended for the method by practicing the recited method step(s). For the purposes of compact prosecution, the method of claim 1 has been interpreted as a method of identifying pain-regulating substances (see the rejection under 35 USC 112, first paragraph) and has been interpreted as a method defined only by the recited method steps (see the rejections under 35 USC 102).

Claims 2-15 and 32-34 depend from claim 1 and thus are indefinite for the same reasons as applied to claim 1.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 and 32-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was made in the Office action mailed 11/1/2005 and has been rewritten to address the amendments to claims 32-34.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

*Nature of the invention:* The claims are drawn to a method for detecting a pain-regulating substance. The positive action method steps require the provision of a cell or preparation from a cell which has synthesized a PIM1-kinase, a protein comprising the amino acid sequence of SEQ ID NO: 2, 4 or 6, a protein that is at least 90%, 95% or 97% homologous to a protein of SEQ ID NO: 2, 4 or 6, a protein encoded by a polynucleotide comprising the nucleic acid sequence of SEQ ID NO: 1, 3 or 5, a protein encoded by a polynucleotide comprising a nucleic acid that is at least 90%, 95% or 97% homologous to a polynucleotide comprising the nucleic acid sequence of SEQ ID NO: 1, 3 or 5, a protein encoded by a nucleic acid that binds under stringent conditions to a polynucleotide comprising the nucleic acid sequence of SEQ ID NO: 1, 3 or 5 or antisense polynucleotides thereof, or a part protein of any of the abovementioned proteins that is at least 10 amino acids long. PIM1 kinase is a serine/threonine kinase. Other than PIM1 kinase, the amino acid sequences of SEQ ID NOS: 2, 4 and 6, and the proteins encoded by the nucleotide sequences of SEQ ID NOS: 1, 3 and 5, the proteins are defined by percent identity. The variants and fragments of PIM1 kinase encompassed by the claims are not required by the claims to have any particular functional activity. Step (a) of claim 1 requires the incubation of a test substance with a cell or preparation of a cell which has synthesized any of the abovementioned proteins or part proteins (hereinafter "protein or part protein"). Step (b) of claim 1 requires the

measurement of binding of the test substance to the protein or part protein or the measurement of at least one functional parameter modified by the binding of the test substance to the protein or part protein. Further, claims 32-34 require the method be repeated with a different protein or part protein, which is a PIM-2 kinase or a PIM-3 kinase.

The claimed methods utilize proteins encoded by nucleic acid molecules, wherein the nucleic acid sequence is defined only by percent identity to PIM-1 or PIM-3. Further, the claimed methods encompass the use of proteins produced by cells containing nucleic acid sequences that encode PIM-1 or PIM-3 "part proteins" of at least 10 amino acids. The sequences are not defined by any function. Although one could make the nucleic acid sequences and cells expressing the proteins defined only by sequence identity and length, one would not know how to use the sequences in an assay to detect pain-regulating substances.

The nature of the invention is complex in that the method is used to identify pain-regulating substances. The specification defines the term "pain-regulating" as relating to a potential regulating influence on the physiological pain event, in particular to an analgesic action or the substance directly or indirectly influences the perception of pain (e.g. paragraphs [0013] and [0021]). The claimed method encompass the identification of a pain-regulating substance as any substance that binds or does not bind to the protein or part protein. Further, the claimed methods encompass the use of any modulation of any function of the protein or part protein to determine if the test substance is a pain-regulating substance. Claims 11 and 12 further limit the step of measuring at least one functional parameter recited in the claims; however, the claims do not limit the direction of modulation (e.g. increased pH or decreased pH). Claims 32-34 require the repetition of the assay with a PIM-2 or PIM-3 protein.

*Breadth of the claims:* The claims are broad in that a broad genus of proteins or part proteins is used in the claimed method. Further, the claims are broad in that they encompass any modification of binding of a test substance or any modification of the protein or part protein by the test substance as a method of detecting a pain-regulating substance. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

*Guidance of the specification and existence of working examples:* The specification states that the starting point for the invention was "the identification of pain-regulated genes which are modified in either expression under pain conditions and are therefore probably involved, via their regulation connections, in the development and processing of chronic pain" (see paragraph [0007]). The specification envisions the interruption of the development of persistent pain, particularly chronic pain, by influencing the function of proteins that are formed to an increased or decreased extent in states of pain (e.g. paragraph [0008]). The specification asserts that PIM1- and PIM3-kinase are regulated by pain or distributed in a pain-relevant manner, with PIM3-kinase having a pain-relevant distribution (e.g. paragraph [0016]). Based upon the modification of the expression or via the expression distribution in an *in vivo* pain model, the specification presumes the PIM1- and PIM3-kinases will have a "strong *in vivo* relevance" (e.g. paragraph [0017]). The specification does not teach how to compare data obtained with PIM-1 kinase to that obtained with PIM-2 or PIM-3 kinase to determine whether a substance is capable of modulating pain.

Example 1 teaches the increase of PIM1 mRNA in the dorsal root ganglion (DRG) of animals injected with complete Freund's adjuvant (CFA), increase of PIM1 mRNA in the dorsal horn and motor neuron areas of the anterior horn after ischiadicus ligature of the rat, increase in

PIM 1 in neuropathic pain regulation in microglia and neurons, and increase in PIM1 protein in the posterior horn in the Chung model (tight ligation and transection of the L(5) spinal nerve) (e.g. paragraphs [00217]-[00219]). Thus, Example 1 discloses the identification of PIM1 kinase as upregulated in pain.

*Predictability and state of the art:* Around the time the invention was made, PIM-1 protein was known to be a serine/threonine kinase with a role in tumorigenesis and cell survival in that PIM-1 kinase acts as to inhibit apoptosis and promote cell survival (Wang et al. J. Vet. Sci. Vol. 2, No. 3, pages 167-179, 2001; e.g. pages 167-170). Further, PIM-1 was known to play a role in hematopoiesis and germ cell maturation (Wang et al.; e.g. page 170). A more recent review of PIM-1 function indicates that PIM-1 binding partners have been identified, many of which are involved in the regulation of cell cycle progression and apoptosis (Bachmann et al. The International Journal of Biochemistry & Cell Biology, Vol. 37, pages 726-730, 2005; e.g. page 728, Biological Functions).

The increased expression of PIM-1 in pain models is correlative and does not necessarily indicate a role for PIM-1 kinase in the sensation of pain. Based upon the teachings discussed above, it is likely that PIM-2 kinase plays a role in apoptosis in the dorsal horn and dorsal root ganglion. At the time the invention was made, the role of apoptosis in neuropathic pain was underdeveloped. Whiteside et al (Journal of Neuroscience Research, Vol. 64, pages 168-173, 2001) teach that in the chronic constriction injury (CCI) model of neuropathic pain, a CCI to the sciatic nerve of adult rats results in an ipsilateral increase in apoptosis in the dorsal horn of the spinal cord (e.g. Abstract; page 168, paragraph bridging columns; page 170, paragraph bridging columns). However, Whiteside et al teach that the role of apoptosis in hyperalgesia is unclear

(e.g. pages 170-172, Does Apoptosis Play a Role in Hyperalgesia?). Apoptosis may be a pathobiological mechanism of chronic pain. Alternatively, the neurons may be eliminated by apoptosis to enhance spinal sensitivity (Whiteside et al; e.g. paragraph bridging pages 171-172). Thus, it would be unpredictable to regulate pain through the regulation of apoptosis. Given the known role of PIM-1 in the prevention of apoptosis, the increased expression may be beneficial; the modulation of PIM-1 kinase may have an effect on cell survival without necessarily acting as an analgesic; or PIM-1 kinase may play a role in the pathobiology of hyperalgesia.

*Amount of experimentation necessary:* The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to use the assay to identify a pain-regulating substance. In order to carry out the invention, it would be necessary for one to confirm that the PIM-1 kinase gene plays a role in pain. For example, one could treat pain model organisms with antisense oligonucleotides to PIM-1 kinase transcript. The reduction in pain observed in antisense treated animals as compared to controls would provide a measure of confidence that one could identify pain-regulating substances. Next, one would have to identify the nucleic acid sequences defined by percent identity or length as compared to the nucleic acid sequence of PIM-1 kinase of human, mouse and rat (SEQ ID NOS: 1, 3 and 5) that are capable of functioning in a manner consistent with the detection of pain-regulating substances. Only when a role for PIM-1 in the pathobiology of pain has been confirmed and variant proteins and functional fragments of PIM-1 kinase have been identified, could one reasonably use the claimed method.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an

undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 1-15 and 32-34 are not considered to be enabled by the instant specification.

***Response to Arguments - 35 USC § 112***

With regard to the rejection of claim 1 and claims that depend therefrom, under 35 U.S.C. 112, second paragraph, Applicant's arguments filed 3/29/2006 have been fully considered but they are not persuasive. The response asserts that one of skill in the art would readily understand the steps required to practice the claimed method, because one would reasonably expect the claimed method to have a reasonable probability of success. The response asserts that one expect the claimed method to result in the identification of pain regulating substances because there is some evidence in the art that certain spinal MAP-kinases are relevant to chronic neuropathic pain models. Specifically, the references of Appendix A indicate that MAP kinase p38 beta is expressed in microglia and when expression of this particular isoform of MAP kinase is reduced, the nociceptive flinching is prevented (e.g. Reference 2). The response does not provide a link between the MAP kinase p38 beta pathway and PIM-1 kinase, and there is no art of record that demonstrates that PIM-1 kinase function is an essential effector of the MAP kinase p38 beta pathway in cold allodynia or other forms of neuropathic pain. Furthermore, Leduc et al (International Immunology, Vol. 12, No. 10, pages 1389-1396, 2000) teach that Pim-1 kinase does not affect signaling through the Ras/Raf/MAP kinase cascade (e.g. Abstract). The response does provide evidence that PIM-1 kinase knock-out rats have a significantly slowed cold allodynia as compared to rats with functional PIM-1 kinase (page 19, Figure 1). At page 19, figure 19 teaches that the PIM-1 knockout rat has fewer paw liftings per 2 min as compared to

rats with two functional PIM-1 alleles. The response indicates that the data is a measure of cold allodynia and asserts that the same result is obtained with PIM-3 kinase. Upon review of Figure 1, it appears as though the knockout rats have fewer paw liftings in response to a cold stimulus; however, the stimulus is not specifically indicated. The lack of experimental detail provided by the response makes it difficult to evaluate the data presented in Figure 1. Thus, it is not clear that performing the claimed method steps will necessarily result in the identification of pain modulating substances. For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With regard to the rejection of claim 7 under 35 U.S.C. 112, second paragraph, the rejection has been withdrawn in view of Applicant's amendment to the claims. The previous rejection of claim 7, as it pertained to the phrase "which allow expression," has been withdrawn.

With regard to the rejection of claim 32 under 35 U.S.C. 112, second paragraph, the rejection has been withdrawn in view of Applicant's amendment to the claims. The previous rejection of claim 32, as it pertained to the phrase "in another part of the method the protein or part protein in steps (a) and (b)," has been withdrawn.

With regard to the rejections of claim 33 under 35 U.S.C. 112, second paragraph, the rejections have been withdrawn in view of Applicant's amendment to the claims. The previous rejections of claim 33 have been withdrawn as they pertained to the phrases "in at least part of the method the protein or part protein in steps (a) and (b) is" and "in another part of the method the protein or part protein in steps (a) and (b)."

With regard to the rejection of claim 34 under 35 U.S.C. 112, second paragraph, the rejection has been withdrawn in view of Applicant's amendment to the claims. The previous

rejection of claim 34, as it pertained to the phrase "in at least part of the method the protein or part protein in steps (a) and (b) is," has been withdrawn.

With regard to the rejection of claim 10, Applicant's arguments, see pages 19-20, filed 3/29/2006, with respect to the rejection of claim 10 have been fully considered and are persuasive. The previous rejection of claim 10, as it pertained to the phrase "via the activity bound thereto from a labeled test substance," has been withdrawn.

With regard to the rejection of claims 1-15 and 32-34 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, Applicant's arguments filed 3/29/2006 have been fully considered but they are not persuasive.

At page 21, paragraph 1, the response asserts that persons of skill in the art would be aware of the relevance of members of the MAP-kinase family with regard to nociception, as evidenced by the literature summarized in Appendix A. All of the references provided in Appendix A have been considered. Reference 5 of Appendix A indicates that the development of drugs based upon mechanistic-based studies of poorly validated molecular targets, including downstream regulators or protein phosphorylation, for use in the pain clinic remains a significant but surmountable challenge as of 2004. While the references (especially reference 2) indicate that MAP kinase p38 beta is expressed in microglia and reduces nociceptive flinching, the response does not provide a link between the MAP kinase p38 beta pathway and PIM-1 kinase. Further, there is no art of record that demonstrates that PIM-1 kinase function is an essential effector of the MAP kinase p38 beta pathway in cold allodynia or other forms of pain. Furthermore, Leduc et al (International Immunology, Vol. 12, No. 10, pages 1389-1396, 2000) teach that Pim-1 kinase does not affect signaling through the Ras/Raf/MAP kinase cascade (e.g.

Abstract). Based upon the evidence provided in Appendix A, one would not have a reasonable expectation of success in identifying modulators of pain using the claimed method.

At page 21, paragraphs 2-3, the response asserts that the results provided in Figure 1 of the response show that PIM-1 kinase has relevance to neuropathic pain. The response does provide evidence that PIM-1 kinase knock-out rats have a significantly slowed cold allodynia as compared to rats with functional PIM-1 kinase (page 19, Figure 1). At page 19, figure 19 teaches that the PIM-1 knockout rat has fewer paw liftings per 2 min as compared to rats with two functional PIM-1 alleles. The response indicates that the data is a measure of cold allodynia. Upon review of Figure 1, it appears as though the knockout rats have fewer paw liftings in response to a cold stimulus; however, the stimulus is not specifically indicated. The lack of experimental detail provided by the response makes it difficult to evaluate the data presented in Figure 1. Moreover, the data presented in Figure 1 are for one type of pain, not necessarily representative of all types of pain encompassed by the claims. Thus, one performing the claimed method steps would not necessarily expect to identify pain modulating substances. Further, the response asserts that the homology of PIM-3 kinase to PIM-1 kinase supports a role for this gene in cold allodynia as well. This is not found persuasive for the reasons set forth above for PIM-1 kinase.

At page 21, paragraphs 4-5, the response assert that the use of broad terminology does not mean a claim is not properly enabled. In the instant case, the claims were not rejected for lack of enablement merely because they encompass a broad range of PIM-1 kinase proteins or part proteins. Each of the Wands factors was considered in making the rejection. While the

breadth of the claims contribute to the complex nature of the subject matter, the evidence as a whole was considered in the rejection presented on pages 8-13 of the prior action.

At page 21 paragraph 6 to page 22, paragraph 2, the response asserts that the stated reasons for the rejection fall outside the test for enablement in that the reasons do not provide an explanation as to why the objective assertions by the applicants in the disclosure should be doubted. This is not found persuasive. Applicant has demonstrated a correlation of increased PIM-1 expression in pain models. The specification does not teach a specific role for PIM-1 in the physiologic response to pain. In fact, the prior art teaches a role for PIM-1 in apoptosis rather than nociception. Other evidence for the unpredictable nature of the invention is provided by Reference 5 of Appendix A (discussed above). Given the underdeveloped and unpredictable nature of the invention. One would have required an undue amount of experimentation to carry out the claimed invention.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-15, 32-34 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Koike et al (FEBS Letters, Vol. 467, pages 17-21, 2000; see the entire reference) as evidenced by Bachmann et al. (The International Journal of Biochemistry & Cell Biology, Vol. 37, pages 726-730, 2005; see the entire reference)

Regarding claims 1, 9 and 47, Koike et al teach plasmid pGLex-Pim-1Δ2, which contains an *Eco*RI-*Pst*I fragment of the human Pim-1 sequence of SEQ ID NO: 1 (see the attached alignment) (e.g. pages 17-18, section 2.2). Koike et al teach the transformation of *Sacharomyces cerevisiae* L40 cells with plasmid pGLex-Pim-1Δ2, and measuring the binding of the test substances, a HeLa MATCHMAKER cDNA library (e.g. page 18, section 2.3). Koike et al teach the measurement of binding by detecting LacZ reporter gene expression, a functional parameter modified by the binding of the test substance to the protein encoded by pGLex-Pim-1Δ2 (e.g. page 18, section 2.3).

Regarding claim 2, the *Sacharomyces cerevisiae* L40 cells are genetically modified with plasmid pGLex-Pim-1Δ2 prior to the incubation of the test substance (e.g. page 18, section 2.3).

Regarding claim 3, the genetic manipulation of the *Sacharomyces cerevisiae* L40 cells with plasmid pGLex-Pim-1Δ2 as taught by Koike et al allows the measurement of the LacZ expression (i.e. functional parameter) because L40 cells contain the LacZ reporter gene. Further, the *Sacharomyces cerevisiae* L40 cells have been genetically manipulated to contain the LacZ gene, which is not found in wild type *Sacharomyces cerevisiae*.

Regarding claim 4, the *Sacharomyces cerevisiae* L40 cells have been genetically modified with the LacZ gene such that LacZ gene expression can be used as a reporter of binding (e.g. page 18, section 3.2).

Regarding claim 7, Koike et al teach the culture of the *Sacharomyces cerevisiae* L40 cells transformed with plasmid pGLex-Pim-1Δ2 such that the Pim-1 fusion protein is expressed (e.g. page 18, section 3.1).

Regarding claim 8, the cells transformed with pGLex-Pim-1Δ2 and the cDNA library are cultured under selective pressure to identify colonies capable of growing on HIis- medium (e.g. page 18, section 3.1).

Regarding claims 11-12, Koike et al teach the measurement of binding by an activation of beta-galactosidase activity as a result of the modification of LacZ gene expression (e.g. page 18, section 2.3).

Regarding claims 5, 9, 13-15, 32-34 and 47, Koike et al teach the transfection of pCMV-FLAG-Pim-1 (containing a sequence consisting of SEQ ID NO: 1, which is 90% identical to SEQ ID NOS: 3 and 5, see the alignment) with pCMV-HP1-HA into human 293T cells (immortalized mammalian cells) and measurement of binding of Pim-1 and HP1 by immunoprecipitation (e.g. page 18, section 2.5). The percent identity between the human/mouse and human/rat proteins is evidenced by page 727, section 2 of Bachmann et al. Bachmann et al indicates that the mouse protein is 94% identical to the human protein, and the rat protein is 97% identical to the human protein.

Regarding claim 6, the nucleic acid sequence of Pim-1 is contained in the recombinant DNA construct of pCMV-FLAG-Pim-1 (e.g. page 18, section 2.5).

Regarding claim 10, the pCMV-HP1-HA plasmid encodes a test substance labeled with an HA tag, and the assay measures the binding of the test substance to the Pim-1 protein (e.g. page 18, section 2.5).

***Response to Arguments***

With regard to the rejection of claims 1-15, 32-34 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Koike et al as evidenced by Bachmann et al, Applicant's arguments filed 3/29/2006 have been fully considered but they are not persuasive.

The response asserts that the claimed invention recites a method for detecting a pain-regulating substance, and Koike et al suggests that pim-1 may have relevance to chromatin dynamics. Thus, the response asserts the reference does not disclose the claimed method of detecting a pain-regulating substance. In response to applicant's arguments, the recitation "for detecting a pain-regulating substance" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). In the instant case, the body of the claim sets forth a complete method, which is anticipated by the teachings of Koike et al.

The response asserts that to qualify as a test substance, the properties of the test substance must be unknown. The response does not point to the instant specification for the definition of the term "test substance," and a definition could not be located upon review of the specification. The term "test substance" has been interpreted broadly to mean any substance, known or unknown. The definition of "test substance" provided by the U.S. Environmental Protection

Agency indicates that a test substance may be a specific form of a chemical substance or mixture that is used to develop data (see Appendix I). Thus, the substances taught by Koike et al are test substances within the metes and bounds of the claim.

The response asserts that the nothing is learned about any test substance by using the method of Koike et al, and that one only learns whether transformation was successful based upon lacZ expression. This is not found persuasive, because the lacZ expression taught by Koike et al is a marker of protein-protein interaction, and thus one learns whether a protein is capable of interacting with Pim-1. Further the response asserts that the teachings of Koike et al do not anticipate an active ingredient of a-h of claim 36. This is not found persuasive, because Koike et al teach a cell comprising a part protein of a protein encoded by a polynucleotide of instant SEQ ID NO: 1.

Thus the teachings of Koike meet each of the claim limitations. For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Applicant's arguments, see pages 24-25, filed 3/29/2006, with respect to the rejection of claims 1-3, 5-7, 9-15, 32-34 and 47 under 35 U.S.C. 102(e) as being anticipated by Reinhard et al have been fully considered and are persuasive. The previous rejection of claims 1-3, 5-7, 9-15, 32-34 and 47 has been withdrawn.

## *Conclusion*

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jennifer Dunston, Ph.D.
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PRIMARY EXAMINER